

The University of Chicago Genetic Services Laboratories



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SLC29A3 Analysis for PHID

Clinical Features

PHID [pigmented hypertrichotic dermatosis with insulin-dependent diabetes mellitus, OMIM#602782] is a rare disorder characterized by childhood onset of pigmented hypertrichotic skin lesions and insulin-dependent diabetes mellitus, which is typically autoantibody negative (1). Circulating insulin is typically not detectable and cannot be induced in response to glucose administration, consistent with a defect of insulin production or secretion, rather than insulin resistance (1). PHID is allelic with H syndrome, which is associated with hyperpigmentation, hypertrichosis, hepatosplenomegaly, heart anomalies, hearing loss, hypogonadism, low height and hyperglycemia (1).

Molecular Genetics

Cliffe *et al* (2009) identified homozygous mutations in the *SLC29A3* gene [OMIM#602782] in five families affected by PHID. *SLC29A3* encodes an equilibrative nucleoside transporter 3 protein, and studies of the *Drosophila* ortholog of this protein have provided evidence that it interacts with the insulin signaling pathway (1). To date, missense, nonsense, splice site and frameshift mutations have been described in the *SLC29A3* gene (1).

Inheritance

PHID is inherited in an autosomal recessive inheritance pattern. Therefore, parents of an affected child are most likely obligate carriers. Recurrence risk for carrier parents is 25%.

Test methods:

Comprehensive sequence coverage of the coding regions and splice junctions of the *SLC29A3* gene is performed. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. The constructed genomic DNA library is sequenced using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All novel and/or potentially pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20bp. Deletion/duplication analysis is performed by oligonucleotide array-CGH. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by array-CGH. Array-CGH will not detect low-level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of this assay may be reduced when DNA is extracted by an outside laboratory.

SLC29A3 sequencing

| | |
|------------------------|--|
| Sample specifications: | 3 to10 cc of blood in a purple top (EDTA) tube |
| Cost: | \$1000 |
| CPT codes: | 81405 |
| Turn-around time: | 4 weeks |

SLC29A3 deletion/duplication analysis

| | |
|------------------------|--|
| Sample specifications: | 3 to10 cc of blood in a purple top (EDTA) tube |
| Cost: | \$1000 |
| CPT codes: | 81404 |
| Turn-around time: | 4 weeks |

Note: The sensitivity of our assay may be reduced when DNA is extracted by an outside laboratory.

Results:

Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

References:

1. Cliffe ST, Kramer JM, Hussain K et al. *SLC29A3* gene is mutated in pigmented hypertrichosis with insulin-dependent diabetes mellitus syndrome and interacts with the insulin signaling pathway. *Hum Mol Genet* 2009; 18: 2257-2265.

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